Bevacizumab to combat EGFR-TKI resistance in a patient with advanced non-small cell lung cancer harboring an EGFR mutation: A case report

ZHIYI WANG, PU ZHOU and GUANGHUI LI

Institute for Cancer Research in People's Liberation Army, Xinqiao Hospital, Third Military Medical University, Chongqing 400037, P.R. China

Received March 29, 2015; Accepted April 25, 2016

DOI: 10.3892/ol.2016.4574

Abstract. Treatment with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) is the first-line strategy for patients with non-small cell lung cancer (NSCLC) harboring EGFR-activating mutations. Acquired resistance to EGFR-TKIs is inevitable in patients receiving EGFR-TKI therapy. Treatment with bevacizumab can induce a marked improvement in the overall and progression-free survival of patients with NSCLC; however, the effect of bevacizumab on TKI resistance in patients with NSCLC with an activating EGFR mutation is largely unknown. The present study reports the case of a patient with advanced, metastatic lung adenocarcinoma harboring 19 Del mutations, and who developed resistance to afatinib. The addition of bevacizumab to afatinib treatment was shown to overcome the acquired TKI resistance in the patient, as well as to promote an improved outcome for her brain metastases.

Introduction

Lung cancer is the leading cause of cancer-induced mortality worldwide, and non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancer cases (1,2). The majority of NSCLC patients already have advanced or metastatic disease at the time of diagnosis (3). Recently, mutations to the EGFR gene were identified in patients with NSCLC and the most commonly found EGFR mutations were deletions in exon 19 and mutations in exon 21 (4). Approximately 10% of these EGFR mutations were detected in Caucasian patients with NSCLC, and 40-60% in Asian NSCLC patients. The disease has been previously associated with sensitivity to the small molecule TKIs (4,5). Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have been used for the treatment of advanced NSCLC harboring EGFR sensitizing mutations, and have been shown to improve progression-free and overall survival in these patients (median overall survival OS, >2 years) (6). In addition, 70% of patients with EGFR sensitizing mutations treated with TKIs achieved a complete or partial response, while only 33% of patients receiving chemotherapy had the same results (7); however, every patient who had initially responded to EGFR-TKI treatment eventually acquired EGFR-TKI resistance, resulting in relapse while still under TKI therapy (8).

Bevacizumab is a recombinant, humanized monoclonal antibody that blocks vascular endothelial growth factor (VEGF) (9). The Eastern Cooperative Oncology Group 4599 study compared the efficacy of treatment with carboplatin/paclitaxel with or without bevacizumab in patients with advanced non-squamous NSCLC (10). The results showed that the use of paclitaxel and carboplatin, combined with bevacizumab resulted in a significant improvement in the median overall and progression-free survival, which marked the start of a new paradigm for the treatment of advanced nonsquamous NSCLC. The JO25567 study, a phase II randomized controlled trail, provided evidence that first-line treatment with a combination of erlotinib and bevacizumab significantly improved the median regression-free survival in patients with nonsquamous NSCLC with activating EGFR mutations (11); however, the effect of bevacizumab on TKI resistance in patients with NSCLC with activating EGFR mutations remains largely unknown. In the present case of metastatic lung adenocarcinoma with acquired EGFR-TKI resistance, the use of bevacizumab with TKI treatment lead to the stabilization of the disease and minimal tumor regression.

Case report

A 53-year-old female patient presented with a cough and hemoptysis in May 2013, without a headache, nausea, vomiting or shortness of breath. A mass was detected in the right inferior lung, with malignant ipsilateral pleural

Correspondence to: Dr Guanghui Li, Institute for Cancer Research in People's Liberation Army, Xinqiao Hospital, Third Military Medical University, 183 Xinqiao Street, Chongqing 400037, P.R. China
E-mail: liguanghui_2000@aliyun.com.cn

Key words: bevacizumab, afatinib, tyrosine kinase inhibitors, epidermal growth factor receptor, NSCLC, acquired resistance

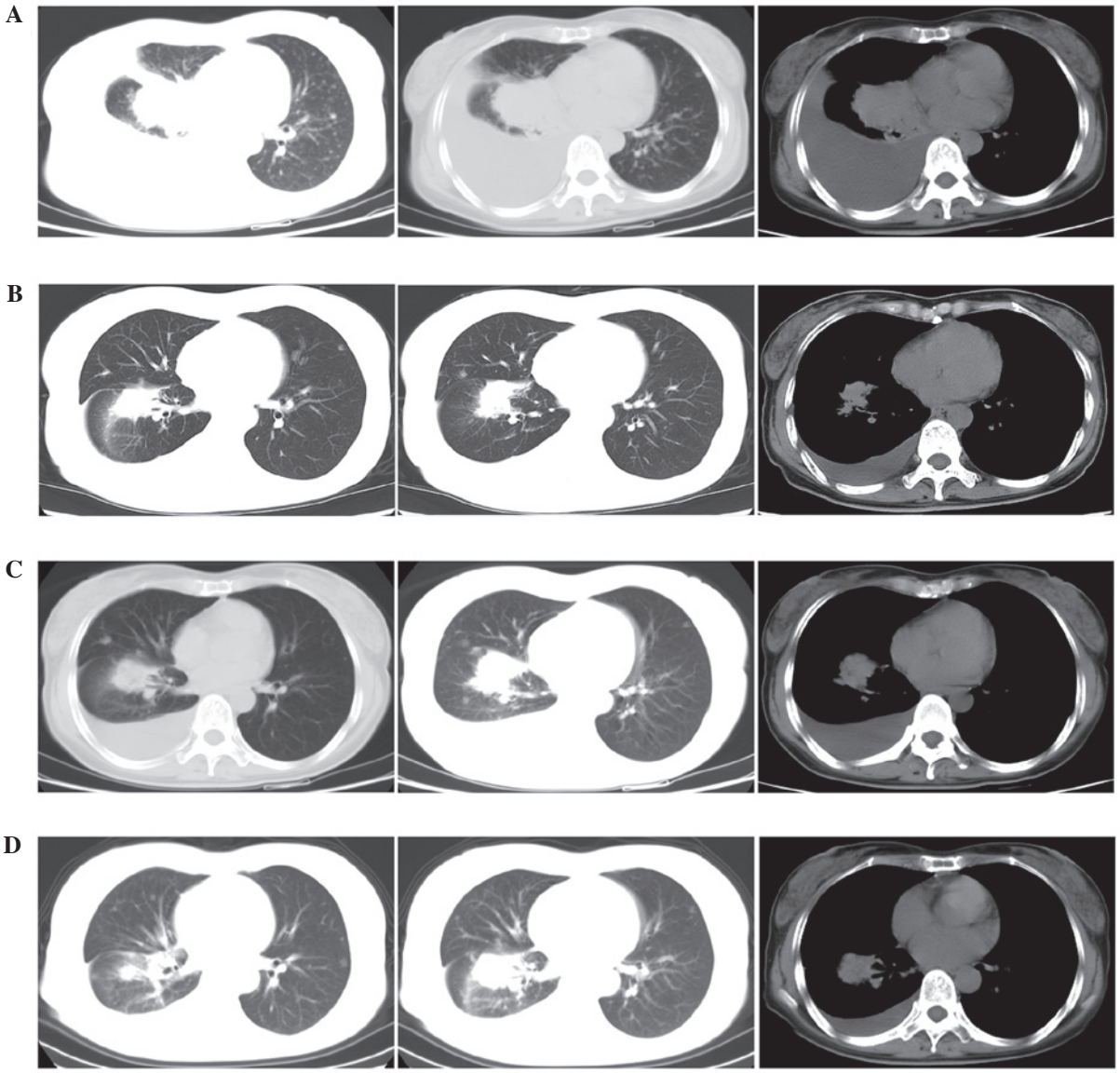

Figure 1. Thoracic computed tomography scans ahowing (A) disease progression prior to afatinib treatment (July 9, 2014), (B) partial response to afatinib treatment (August 27, 2014) and (C) disease progression following 3 months of afatinib treatment (October 8, 2014). (D) The right lung lesion and pleural effusion were shown to have shrunk and stabilized following the addition of bevacizumab to afatinib treatment (January 14, 2015).

effusion and multiple brain metastases (BM) in bilateral lobes, as well as mediastinal and supraclavicular lymph nodes upon thoracic computed tomography (CT) and whole-body positron emission tomography/CT, performed in Shenzhen People's Hospital (Shenzhen, China). The patient was referred to Xinqiao Hospital (Chongqing, China) and a core biopsy of the mass in the right lung was performed, confirming a moderate differentiated adenocarcinoma. Scorpion/Amplification Refractory Mutation System EGFR mutation test detected an EGFR exon 19 deletion in tumor cells. The patient was started on first-line treatment with EGFR-TKI on June 2013 and developed a partial response, according to chest CT evaluation; however, after 8 months of EGFR-TKI treatment, a thoracic CT scan confirmed disease progression in the lung lesion. Second line chemotherapy (pemetrexed, 500 mg/m^2 plus cisplatin, 75 mg/m^2) was initiated on 28 February 2014, and cell biological treatment was administered in Daping Hospital (Chongqing, China). Following four cycles of chemotherapy, the patient's symptoms worsened and she experienced headaches, dizziness and worsening neurological symptoms of speech and left-sided limb impairment. Radiographic evaluation showed disease progression in the lung lesion and pleural effusion (Fig. 1A), and new multiple brain metastases (Fig. 2A); therefore, treatment with the second-generation TKI afatinib (40 mg/day) and concurrent whole-brain radiotherapy (WBRT; 30 Gy/10F/2W) was initiated on July 2014. A partial radiographic and clinical response of the mass in the primary right lobe and metastases in the lung, pleura (Fig. 1B) and brain (Fig. 2B) was achieved. After 3 months of treatment with afatinib, disease progression was detected in the right lung lesion and pleural effusion (Fig. 1C), while the BM remained stable (Fig. 2C).

The patient refused to receive re-biopsy and additional chemotherapy. Combination treatment with bevacizumab and afatinib was recommended and approved by the patient;

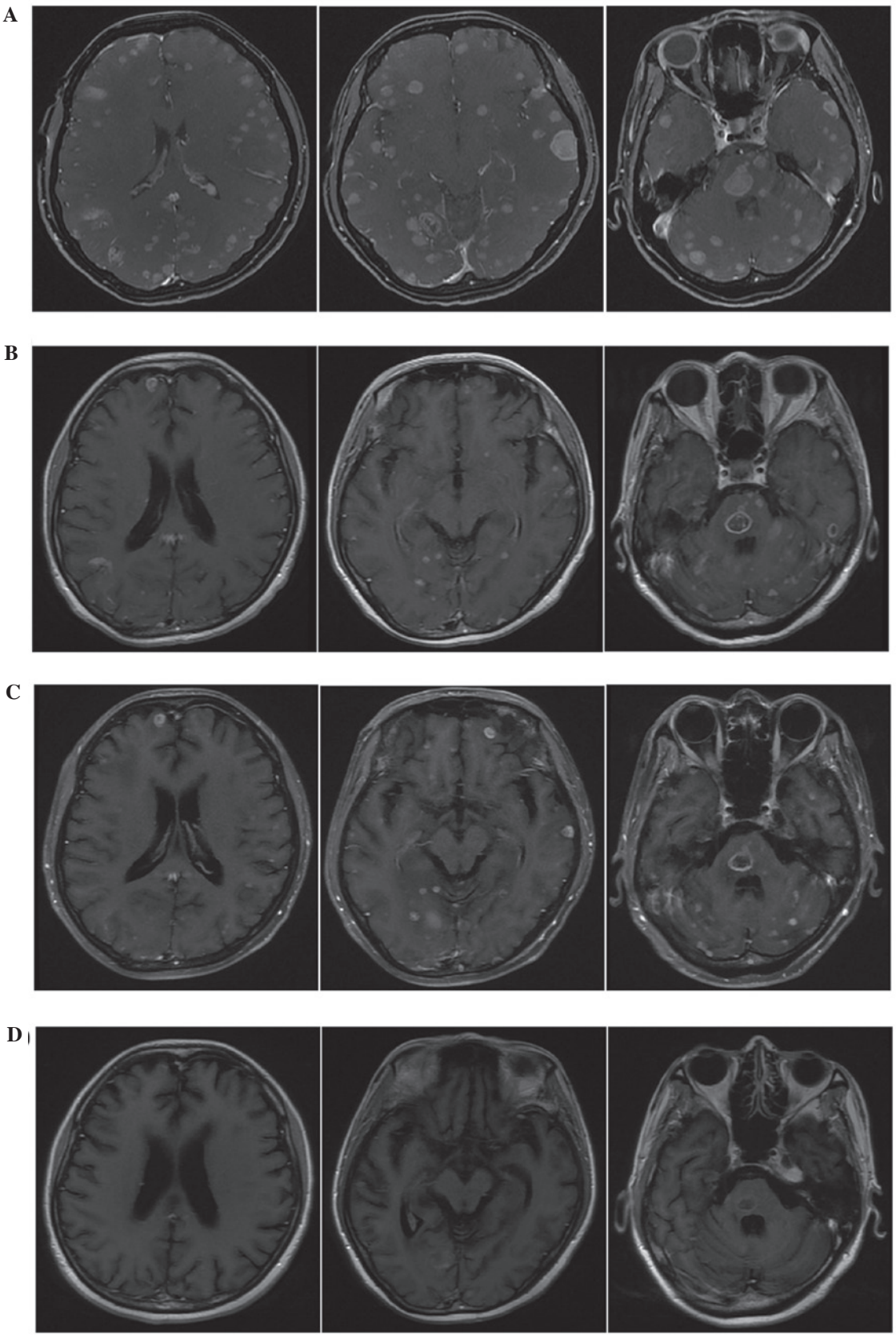

Figure 2. Contrast-enhanced MRI scans of the brain showing (A) multiple BM prior to afatinib treatment (July 9, 2014) and (B) partial response to afatinib treatment with concurrent whole-brain radiotherapy (August 27, 2014). (C) BM remained stable after 3 months of afatinib therapy (October 8, 2014). (D) Marked partial response was observed in the BM following the addition of bevacizumab to afatinib treatment (January 14, 2015).

treatment with bevacizumab (7.5 mg/kg once every 2 weeks) by intravenous infusion was commenced in Xinqiao Hospital on October 9, 2014, combined with continued therapy of afatinib (40 mg/day). No hypertension, hemorrhage or proteinuria was

recorded during the treatment. After 1 month of treatment, thoracic CT and brain magnetic resonance imaging (MRI) scans showed shrinkage of the mass in the right lung and BM, as well as a right pleural effusion reduction. At the time of writing, the patient remained under combination therapy with afatinib with bevacizumab, and the right lung mass, BM and pleural effusion were shown to be stable on follow-up CT (Fig. 1D) and MRI scans (Fig. 2D). No serious adverse events occurred throughout the treatment period, and the patient had a good quality of life.

Discussion

To date, no previous reports have been published on the use of bevacizumab against EGFR-TKI resistance in patients with activating EGFR mutations. To the best of our knowledge, the present study is the first to report combination treatment with bevacizumab and afatinib overcoming acquired EGFR-TKI resistance.

EGFR-TKIs have been shown previously to have a positive effect on patients with advanced NSCLC with EGFR activating mutations, and are therefore used as first-line treatment for this condition (12-14); however, treatment with EGFR-TKI is not curative; tumor cells inevitably develop EGFR-TKI resistance, which leads to disease progression. Additionally, it has been shown that the major resistance mechanisms are due to T790M point mutation on EGFR exon 20 (15). The third-generation EGFR-TKIs that are able to overcome T790M-mediated resistance to EGFR inhibitors in lung cancer are still being studied in clinical trails (16). The JO25567 phase 2 trial showed that combination treatment with erlotinib and bevacizumab significantly improved the progression-free survival of patients with NSCLC with activating EGFR mutations, as compared with erlotinib alone (11); however, no evidence has demonstrated that the addition of bevacizumab to TKI treatment can reverse acquired TKI resistance in NSCLC; the findings of the JO25567 trial implied that bevacizumab can postpone the resistance of tumor cells to TKI. In the present case, the lung and pleural lesions developed a resistance to afatinib, but shrank following the administration of combination treatment with bevacizumab and afatinib. In addition, follow-up CT and MRI scans showed that the lesions remained stable on, which suggests that the addition of bevacizumab helped overcome TKI resistance in patients with NSCLC harboring EGFR activating mutations.

WBRT remains the cornerstone of treatment for multiple central nervous system metastases caused by NSCLC. Lately, a therapeutic effect of EGFR-TKI in BM harboring EGFR-activating mutations has been demonstrated (14,17). The concomitant use of EGFR-TKI and radiotherapy plays an important role in patients with multiple, symptomatic BM due to NSCLC harboring EGFR mutations (18). The effect of combined treatment with TKIs and WBRT against BM was observed in the present patient. An MRI scan following treatment with afatinib and concurrent WBRT confirmed that a marked partial response of the BM had been achieved.

Bevacizumab in combination with chemotherapy has shown a significant survival benefit in NSCLC, and has been approved for the treatment of patients with locally advanced or metastatic non-squamous NSCLC (10). Due to concerns regarding the risk of central nervous system hemorrhage, patients with BM had previously been largely excluded from clinical trials involving bevacizumab; however, it has since been demonstrated that anti-angiogenic therapy with bevacizumab is safe for patients with BM (19,20). Bevacizumab is a humanized anti-vascular endothelial growth factor monoclonal antibody. Questions on whether bevacizumab is capable of penetrating the brain-blood barrier and having a certain effect on NSCLC-induced BM have arisen. In the present study, MRI scans showed that the BM remained stable under treatment with afatinib; however, the addition of bevacizumab to afatinib treatment achieved further shrinkage of the BM, which suggests that the combination of EGFR-TKI and bevacizumab could achieve a favorable outcome for patients with BM caused by nonsquamous NSCLC habouring EGFR activating mutation.

In conclusion, the addition of bevacizumab to afatinib treatment can tackle TKI resistance and promote a better outcome for patients with NSCLC-induced BM with EGFR activating mutations; however, further studies are required to confirm these findings.

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